ACTH, corticosterone, and prolactin levels and decreases DA and NE levels in hypothalamic regions. This stressor attenuates nicotine's activation of NE neurons but does not reverse its attenuating effects on prolactin.

Nicotine appears to be associated with neuroendocrine activity by NE and DA activation (Fuxe et al. 1987). Immunohistochemical studies suggest that alterations in NE function are more important for the control of the pituitary-adrenal-axis, while DA turnover appears to be crucial for nicotine's effects on prolactin, LH, and follicle-stimulating hormone (FSH). Moreover, these studies indicate that similar nAChRs are located within both DA mesolimbic and neostriatal systems.

Stimulation of Pituitary Hormones

Nicotine administration and cigarette smoking stimulate the release of several anterior and posterior pituitary hormones. Seyler and coworkers (1986) had human subjects smoke two high-nicotine (2.87 mg) cigarettes in quick succession. Plasma levels of prolactin, ACTH, β-endorphin/β-lipoprotein, growth hormone (GH), vasopressin, and neurophysin I increased. No change was seen in TSH, LH, or FSH. The rapid smoking paradigm used by Seyler and coworkers (1986) may have contributed to the effects of nicotine. Growth hormone levels exhibited a prolonged increase after subjects smoked three cigarettes in rapid succession (Sandberg et al. 1973). In experiments conducted by Winternitz and Quillen (1977) with male habitual smokers, GH began to rise after two cigarettes, peaked at 1 hr, and then returned to control levels while smoking continued. Wilkins and colleagues (1982) also found that smoking increases GH levels and presented evidence that the effect is nicotine mediated. Coiro and coworkers (1984) reported that the increase in GH produced by clonidine was greatly enhanced by cigarette smoking, suggesting that nicotinic cholinergic and adrenergic mechanisms might interact in the stimulation of GH secretion.

The TSH plasma levels were not affected when nicotine was administered over a 60-min period to female rats (Blake 1974). In studies involving exposure to cigarette smoke, Andersen and colleagues (1982) reported a lowering of TSH secretion in rats, but as noted, Seyler and coworkers (1986) found no change in human subjects. Thus, the data on the effects of nicotine on TSH release are inconclusive at this time.

ACTH plasma levels increased after i.p. injection of nicotine in the rat (Conte-Devolx et al. 1981). In similar experiments, Cam and Bassett (1983b) found that elevated ACTH levels peaked and rapidly declined to a sustained plateau level. Sharp and Beyer (1986) reported that the effects of nicotine on ACTH in rats show a rapid and marked desensitization. Seyler and coworkers (1984) had male

subjects smoke cigarettes containing 0.48 or 2.87 mg of nicotine. No increases in ACTH or cortisol were detected after subjects smoked 0.48-mg-nicotine cigarettes. Cortisol levels rose significantly in 11 of 15 instances after smoking the high-nicotine cigarettes, but ACTH rose in only 5 of the 11 instances when cortisol increased. Each ACTH increase occurred in a subject who reported nausea and was observed to be pale, sweaty, and tachycardic. Seyler and coworkers (1984) studied smokers and concluded that ACTH release occurs only in smokers who become nauseated.

LH levels were reduced in male rats exposed to unfiltered cigarette smoke, while FSH was unchanged (Andersen et al. 1982). In experiments by Winternitz and Quillen (1977), there were no differences in LH and FSH among male cigarette smokers while smoking as compared with not smoking. Seyler and colleagues (1986) found no change in human LH or FSH levels after smoking. There is no evidence of gonadotropin release stimulated by nicotine or smoking.

Prolactin plasma levels were lowered considerably in lactating rats injected twice daily with nicotine (Terkel et al. 1973). It was suggested that failure of prolactin release following chronic nicotine administration was responsible for low milk production and starvation of pups. Blake and Sawyer (1972) found that, in lactating rats, the rapid suckling-induced release of prolactin into the blood is inhibited by s.c. injections of nicotine. Ferry, McLean, and Nikititovich-Winer (1974) reported that tobacco smoke inhalation in rats delays the suckling-induced release of prolactin. Andersen and coworkers (1982) found that prolactin secretion was reduced in male rats in a dose-dependent manner by exposure to unfiltered cigarette smoke. However, Sharp and Beyer (1986) reported that the effects of nicotine on prolactin in rats shows a biphasic effect, first increasing and then decreasing. Suppressed prolactin levels were found in female smokers who were breast feeding (Andersen et al. 1982). These researchers noted that smokers weaned their babies significantly earlier than nonsmokers. However, Wilkins and coworkers (1982) observed an increased level of prolactin in male chronic smokers.

Arginine Vasopressin

In addition to its antidiuretic effects, arginine vasopressin acts as a vasoconstrictor (Munck, Guyre, Holbrook 1984; Waeber et al. 1984). Arginine vasopressin may also act as a neuromodulator in pathways that affect behavior. It has been shown to promote memory consolidation and retrieval in rats (Bohus, Kovacs, de Wied 1978) and there are reports of memory enhancement following intranasal administration of a vasopressin analog in both normal and memory-deficient humans (LeBoeuf, Lodge, Eames 1978; Legros et al. 1978;

Weingartner et al. 1981). Nicotinic cholinergic receptors in the medial basal hypothalamus and muscarinic cholinergic receptors in the neurohypophysis (posterior pituitary) have been implicated in the release of vasopressin (Gregg 1985). Nicotine has been found to stimulate vasopressin release in a dose-related manner in animals (Reaves et al. 1981; Siegel et al. 1983) and in humans (Dietz et al. 1984; Pomerleau et al. 1983; Seyler et al. 1986). These observations are consistent with the effects of nicotine on cognitive performance (Chapter VI).

The Pro-Opiomelanocorticotropin Group of Hormones

The POMC hormones are released in response to stress and in response to corticotropin-releasing hormone (Munck, Guyre, Holbrook 1984; Krieger and Martin 1981). ACTH has behavioral effects and stimulates the release of steroids such as cortisol from the adrenal cortex. ACTH produces rapid cycling between sleeping and waking as well as sexual stimulation, grooming/scratching, blocking of opiate effects such as analgesia, and the enhancement of attention and stimulus discrimination (Bertolini and Gessa 1981). Endogenous opioids, such as β-endorphin, potentiate vagal reflexes, cause respiratory depression, lower blood pressure, block the release of catecholamines (Beaumont and Hughes 1979; Schwartz 1981), have antinociceptive effects (van Ree and de Wied 1981), and modulate neurotransmitter systems leading to amnesic effects (Izquierdo et al. 1980; Introini and Baratti 1984). It has been suggested that the primary function of the endogenous opioids is metabolic, serving to conserve body resources and energy (Amir, Brown, Amit 1980; Margules 1979; Millan and Emrich 1981).

Nicotine appears to stimulate the release of corticotropin-releasing hormone from the hypothalamus through a nicotinic cholinergic mechanism (Hillhouse, Burden, Jones 1975; Weidenfeld et al. 1983). Using an isolated perfused mouse brain preparation, Marty and coworkers (1985) demonstrated that nicotine stimulates secretion of β-endorphin and ACTH in a dose-related manner when applied directly to the hypothalamus but not when applied to the pituitary. The work of Sharp and Beyer (1986) supports this finding; they reported that the secretion of ACTH following nicotine was unaffected by adrenalectomy. Nicotine administration to rats has also been shown to increase the plasma levels of corticosterone, ACTH, and β-endorphin in a dose-related manner (Conte-Devolx et al. 1981). Termination of chronic nicotine administration reduced hypothalamic β-endorphin levels (Rosecrans, Hendry, Hong 1985). Hurlick and Corrigal (1987) have also observed that the narcotic antagonist naltrexone inhibits some nicotine-modulated behavior in mice, providing a possible link between nicotine stimulation of endogenous opioid activity and behavioral responses. Acute administration of

nicotine increases levels of plasma ACTH and corticosterone sharply (Cam and Bassett 1983b), while chronic exposure results in complete adaptation (Cam and Bassett 1984). Melanocyte-stimulating hormone was decreased and β-endorphin was increased by i.p. injections of nicotine in the rat (Conte-Devolx et al. 1981).

Risch and colleagues (1980, 1982) have accumulated evidence for cholinergic control of cortisol, prolactin, and β-endorphin release in humans. Rapid smoking increases circulating cortisol, β-endorphin, and neurophysin I (Pomerleau et al. 1983; Seyler et al. 1984; Novack and Allen-Rowlands 1985; Novack, Allen-Rowlands, Gann, in press). Moreover, in a study that examined the role of endogenous opioid mechanisms in smoking, Tobin, Jenouri, and Sackner (1982) observed that mean inspiratory flow rate increases during the smoking of a cigarette but is depressed shortly after smoking. Naloxone had no effect on the initial stimulation of respiration in response to smoking but did significantly blunt the subsequent depression of respiration. The significance of these findings for the control of cigarette smoking remains equivocal (Karras and Kane 1980; Nemeth-Coslett and Griffiths 1986; Chapter IV).

Thyroid

Most of the earlier work (1930s through 1950s) assessing the effects of nicotine on thyroid function involved histological studies of the thyroid glands from animals treated chronically with nicotine. The findings are inconsistent in that some studies suggest elevated thyroid activity and others do not (Cam and Bassett 1983a). In a more recent study of nicotine's action on the plasma levels of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), Cam and Bassett (1983a) found that a single i.p. injection of 200 μg/kg did not alter the level of either hormone, although it did produce an increase in plasma corticosterone. As mentioned earlier, nicotine does not consistently affect TSH in animals or humans (Blake 1974; Seyler et al. 1986).

Adrenal Cortex

Several studies in animals and human subjects have reported that nicotine and cigarette smoking lead to elevated levels of corticosteroids. Kershbaum and colleagues (1968) administered nicotine i.v. to anesthetized dogs and found a 64 percent rise in plasma corticosteroids. In rats, corticosteroid concentrations increased 50 percent after i.p. administration of nicotine. Suzuki and coworkers (1973) also reported adrenal cortical secretion in response to nicotine in conscious and anesthetized dogs. The effects of nicotine on plasma corticosteroids in stressed and unstressed rats were studied by Balfour, Khuller, and Longden (1975). The administration of nicotine to unstressed rats caused a rise in corticosterone which persisted for

60 min. Nicotine did not affect plasma corticosterone concentration in rats stressed by being placed on an elevated platform. Other studies showed increased plasma corticosteroid levels after nicotine administration (Turner 1975; Cam, Bassett, Cairncross 1979; Cam and Bassett 1983b). Andersen and colleagues (1982) exposed male rats to unfiltered cigarette smoke and found a dose-related increase in corticosterone secretion. Filtered cigarette smoke was inactive.

Seifert and coworkers (1984) found that the chronic administration of 0.5 or 1.0 mg/kg of nicotine s.c. twice daily for 8 weeks to rats produced a marked decrease in plasma aldosterone levels. In this study, nicotine had no effect on plasma corticosterone concentration.

Hokfelt (1961) reported increases in plasma cortisol and urinary 17-hydroxycorticosteroids following cigarette smoking in human subjects. Kershbaum and coworkers (1968) reported similar results involving elevations of 11-hydroxycorticosteroids. Hill and Wynder (1974) found that serum corticosteroids were markedly elevated after high-nicotine (2.73 mg) cigarettes were smoked. No increase was seen with cigarettes containing less nicotine. Cryer and colleagues (1976) also found an increase in circulating levels of corticosteroids after smoking. Winternitz and Quillen (1977) reported a sharp increase in circulating cortisol after two cigarettes. The levels were maintained through the smoking period and fell gradually to normal. Wilkins and coworkers (1982) also observed increased levels of cortisol after 2-mg-nicotine cigarettes were smoked. No increases in cortisol were detected after smoking 0.48-mg-nicotine cigarettes, but cortisol rose significantly in 11 of 15 cases smoking 2.87-mg-nicotine cigarettes (Seyler et al. 1984). Consistent with these results is the observation of Puddey and colleagues (1984) that cessation of smoking is associated with a significant fall in cortisol levels.

In contrast to these findings, Tucci and Sode (1972) reported intact diurnal circadian variations of cortisol and unchanged 24-hr 17-hydroxycorticosteroids during smoking. Benowitz, Kuyt, and Jacob (1984) studied 10 subjects who either smoked their usual brand of cigarettes, some of which contained 2.5 mg nicotine, or abstained. Plasma cortisol concentrations throughout the day did not differ during smoking or abstaining. Thus, while the majority of human and animal data indicates that nicotine or smoking elevates corticosteroid levels, the effects appear to be influenced by dose, time, and perhaps other factors.

Many investigators cited above have proposed that nicotine's effects on corticosteroids are mediated by the release of ACTH. Indeed, hypophysectomy abolished the increase in adrenocortical secretion following nicotine administration (Suzuki et al. 1973; Cam, Bassett, Cairncross 1979) and nicotine-induced increase in plasma ACTH precedes the increase in cortisol (Conte-Devolx et al. 1981). However, Turner (1975) found that bilateral adrenal demedullation

abolished the rise in corticosterone in response to nicotine and suggested that the effect of nicotine is mediated via adrenal release of catecholamines and that centrally mediated stimulation is not significant. In contrast, the work of Matta and associates (1987) demonstrates that the effects of nicotine on ACTH secretion are centrally mediated. Rubin and Warner (1975) have also shown that nicotine directly stimulates isolated adrenocortical cells of the cat. The stimulant effect was dose-dependent and required the presence of calcium. These experiments also indicated that nicotine enhances the steroidogenic effect of ACTH.

Androgens

In male beagles, chronic smoking of high-nicotine/tar cigarettes was associated with decreased activity of 7α-hydroxylase active on testosterone (Mittler, Pogach, Ertel 1983). Testicular 6β- and 16α-hydroxylases were not altered, while the hepatic androgen 6β-hydroxylase activity in the testis was stimulated markedly by smoking. Serum testosterone levels were reduced to 54 percent of control levels by heavy smoking. It was concluded that chronic cigarette smoking increased hepatic metabolism of testosterone, resulting in lowered serum testosterone levels. However, it may be that total testosterone is lower while free testosterone is not.

Estrogens

Cigarette smoking is associated with antiestrogenic effects in women, including earlier menopause, lower incidence of breast and endometrial cancer, and increased osteoporosis. MacMahon and colleagues (1982) reported lower urinary estrogen levels in premenopausal smokers than in premenopausal nonsmokers and suggested that the low estrogen secretion reflected lower estrogen production, based on decreased estrone, estradiol, and estriol. However, 2-hydroxyestrogens, the major metabolites of estradiol in women, were not measured. Jensen, Christiansen, and Rodbro (1985) presented evidence for increased hepatic metabolism of estrogens as a result of smoking based on an observation of decreased serum estrogen levels in postmenopausal smokers receiving exogenous hormone therapy. This study examined 136 women treated for 1 year with different doses of estrogen. Reduction of serum estrogen was most pronounced in the highest estrogen-dose group. There was a significant inverse correlation between the number of cigarettes smoked daily and changes in serum estrogen. Michnovicz and colleagues (1986) found a significant increase in estradiol 2-hydroxylation in premenopausal women who smoked at least 15 cigarettes/day. They concluded that smoking exerts a powerful inducing effect on the 2-hydroxylation pathway of estradiol metabolism, which is likely to lead to decreased bioavailability of hormone at estrogen target tissues.

Pancreas and Carbohydrate Metabolism

The body weight of smokers is consistently lower than that of nonsmokers, and smokers tend to gain weight after cessation of smoking (see Chapter VI for a detailed discussion of these relationships). These phenomena are thought to contribute to tobacco use. Glauser and coworkers (1970) and Hofstetter and coworkers (1986) suggested that a change in metabolic rate is partially responsible for these effects. Schechter and Cook (1976) and Grunberg, Bowen, and Morse (1984) showed that rats which were administered nicotine lost body weight without reducing food intake, although the body weight changes were not as great as when eating behavior declined as well (Grunberg 1982). Grunberg (1986) has pointed out that differences in body weight between smokers and nonsmokers result from changes in energy consumption (via changes in specific food consumption) and changes in energy utilization. Recently, Grunberg and coworkers (1988) have reported reductions of insulin levels accompanying nicotine administration in rats which could result in an increase in the utilization of fat, protein, and glycogen. This finding is consistent with work of Tjälve and Popov (1973), using rabbit pancreas pieces, and studies by Florey, Milner, and Miall (1977) of human smokers versus nonsmokers. Grunberg and coworkers (1988) have suggested that the effects of nicotine on insulin levels also may be involved in the nicotine-induced decrease of sweet food preferences.

Electrophysiological Actions of Nicotine

Electrocortical Effects

The brain responds to electrical as well as to chemical stimuli. Therefore, measurements of the electrophysiological actions of nicotine complement studies of its chemical effects. In addition, electrophysiological activity reflects function that may relate to sensory and cognitive changes observed in humans after smoking (see Chapter VI). In animals, nicotine produces changes ranging from subtle latency decreases in the primary auditory pathway to seizures. The electrophysiological actions of nicotine may help to relate the anatomical and receptor data (discussed earlier in this Chapter) with sensory and cognitive data (discussed in greater detail in Chapter VI).

The human studies on electrocortical effects of nicotine have some methodological limitations. Most of the human studies had subjects smoke cigarettes and did not measure blood levels of nicotine. Also, most studies were performed on smokers whose immediate and long-term smoking history was determined by questionnaires which may not accurately reflect tolerance and physical dependence (Chapter IV). In some studies the subjects were deprived of cigarettes, but no objective measures such as expired carbon monoxide or blood

nicotine levels were collected to verify compliance with the deprivation conditions.

Spontaneous Electroencephalogram

Historically, nicotine and ACh were used in animal experiments to study the cholinergic mechanisms in the midbrain and thalamus which produced EEG and behavioral activation (Longo, von Berger, Bovet 1954; Rinaldi and Himwich 1955a,b). The administration of nicotine produced EEG activation, consisting of desynchronized low-voltage, fast activity, and behavioral arousal or alerting. These EEG and behavioral responses resembled those produced by electrical stimulation of the midbrain reticulomesencephalic activating system (Moruzzi and Magoun 1949). With the discovery by Eccles, Eccles, and Fatt (1956) of nicotinic receptors in the Renshaw cell of the spinal cord, other investigators began to study the precise pharmacology of the EEG and behavioral alerting produced by nicotine and electrical stimulation of the midbrain. Cigarette smoking in humans also produced EEG desynchronization (Hauser et al. 1958; Wechsler 1958; Bickford 1960) or EEG desynchronization with an increase in alpha frequency (Lambiase and Serra 1957). By the late 1950s and early 1960s it was generally known that nicotine or tobacco smoke caused EEG and behavioral arousal in animals and humans, but several important issues were unresolved.

The central effects of nicotine were originally thought to result from its action on the cardiovascular system (Heymans, Bouckeart, Dautrebande 1931). Early studies found that EEG desynchronization occurred when the subjects smoked nicotine cigarettes, nicotine-free cigarettes, or sucked on glass tubes filled with cotton (Hauser et al. 1958; Wechsler 1958). Schaeppi (1968) injected nicotine into the vertebral artery, carotid artery, and third and fourth ventricles of a cat's brain and was able to dissociate the effects of nicotine on the EEG from those on the cardiovascular system. Kawamura and Domino (1969) demonstrated that the EEG changes induced by nicotine could be obtained in animals whose blood pressure increase was blocked. Prevention of release of catecholamines in reserpine-pretreated animals did not interfere with the EEG desynchronization produced by nicotine (Knapp and Domino 1962).

Inhaled tobacco smoke (2-mL samples with about 2 μg/kg of nicotine) and 2 μg of nicotine injected every 30 sec in a cat encephale isolé preparation produced EEG desynchronization. EEG and behavioral activation after cigarette smoke inhalation was also observed in unanesthetized cats with implanted electrodes (Hudson 1979). Lukas and Jasinski (1983) found that i.v. doses (0.75 to 3.0 mg) in human smokers resulted in dose-dependent decreases in alpha (8 to 12 Hz EEG activity) power and EEG desynchronization. In an inpatient study where nicotine deprivation was carefully controlled and

monitored by measurement of expired carbon monoxide, the smoking of non-nicotine cigarettes did not change the EEG (Herning, Jones, Bachman 1983), but EEG changes did occur when subjects smoked nicotine-containing cigarettes. These studies confirm that nicotine has a direct action on the CNS separate from the cardiovascular effects and that the effects are produced primarily by the nicotine in inhaled tobacco smoke.

As experimental physiological manipulations, EEG recording, and EEG quantification techniques improved, the specific nature of the nicotine-induced cortical EEG changes and their relationship to behavior were found to be more complex than originally thought. The desynchronization produced by nicotine (20 to 100 μg/kg) in the cat was blocked by anterior pontine transections, but not by midpontine transections (Knapp and Domino 1962). The midbrain reticular activating system was needed for the cortical EEG desynchronization produced by nicotine. However, larger doses of nicotine injections also produced synchronous slow high-voltage EEG activity in the hippocampus (hippocampal theta). Injections of the muscarinic agonist arecoline (20 to 40 mg/kg) in the anteriorly transected midbrain preparations still produced the hippocampal theta activity without the cortical desynchronization. Atropine (1 mg/kg) and mecamylamine (1 mg/kg), but not the ganglionic antagonist trimethidinium (1 mg/kg) block the nicotine induced EEG desynchronization in an intact animal. The convulsions observed after nicotine injections (1 to 5 mg/kg in cats; 0.05 to 0.25 μg/g in mice) (Laurence and Stacey 1952; Stone, Meckelnburg, Torchiana 1958; Stümpf, Petsche, Gogolák 1962; Stümpf and Gogolák 1967) appear to be due to nicotine's ability in large doses to stimulate muscarinic cholinergic receptors in the hippocampus. Because a high concentration of labeled nicotine binds to hippocampal cells of the cat (Schmiterlöw et al. 1967) and areas adjacent to the hippocampus in the rat (Clarke, Pert, Pert 1984), the possibility that nicotine-induced limbic electrical activity contributes to its behavioral effects cannot be discounted.

Nicotine's alerting effect on the brain may also involve a peripheral component. Electrocortical and behavioral arousal occurs in the cat within 1 to 2 sec after injection of 10 to 15 μg/kg into the right atrium of the heart, originating in vagal pulmonary C fiber afferents (Ginzel 1987). The human counterpart to this finding is the observation by Murphree, Pfeiffer, and Price (1967) that an initial EEG change occurred within 5 sec after cigarette smoke inhalation, which is shorter than a chest-to-head circulation time. Another input from the periphery arises from nicotinic sites in the arterial tree. Injection of small amounts (2 to 4 μg/kg) of nicotine, even as far away from the brain as into the lower aorta or femoral artery, causes instantaneous arousal from all types of sleep (Ginzel and Lucas 1980).

The nicotine-induced release of ACh (MacIntosh and Oborin 1953; Mitchell 1963) may be responsible for the EEG desynchronization in animals (Armitage, Hall, Sellers 1969). The effect does not appear to be due to the direct action of nicotine on the cortex because the cortical cholinergic receptors are largely muscarinic (Kuhar and Yamamura 1976; Rotter et al. 1979). Lower doses of nicotine (20 μg/kg/30 sec for 20 min) induced EEG desynchronization and ACh release in the cat, whereas higher doses (40 μg/kg/30 sec for 20 min) produced either an increase or decrease in EEG desynchronization with corresponding increase or decrease in ACh release (Armitage, Hall, Sellers 1969). The effect of nicotine on the EEG was short lived relative to the release of ACh. Two separate pathways have been proposed to explain these results: an ascending cholinergic pathway mediating the cortical desynchronization and a limbic pathway mediating the ACh release.

In one strain of mice, C57BL, nicotine increased cortical high-voltage activity and decreased homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenthyleneglycol (MHPG) production in a perfused brain preparation (Erwin, Cornell, Towell 1986). The decrease in HVA and MHPG levels reflects an increase in brain DA and NE levels. In intact C57BL mice, nicotine decreased locomotor activity (Marks, Burch, Collins 1983a). Thus, at least in one strain of mice, nicotine induces an increase in cortical EEG synchronization, a decrease in locomotor activity, and an increase in brain catecholamines. Little evidence relates the cortical desynchronization observed in animals and humans to an increase in catecholamine changes in the brain.

As trends in neuroscience research have shifted away from spontaneous EEG recording in animals to intracellular recording, receptor localization, and binding techniques, the precise quantification of the nicotine-induced EEG desynchronization and hippocampal synchronization has not been done. This type of quantification has been done in humans by power spectral analysis. This technique quantifies the EEG by the distribution and amplitude of brain waves at different frequencies. Alpha power includes EEG activity in the 8- to 12-Hz frequency range. Theta power includes EEG activity in the 4- to 7-Hz frequency range. Beta power includes EEG activity in the frequency range of 13 Hz and higher.

The comparison of nicotine-induced EEG changes in animals and humans is complicated by an important methodological difference. Animals usually have not previously been given nicotine, while in studies of humans, the subjects always are experienced tobacco smokers. Moreover, in human studies that included a deprivation period, nicotine abstinence may have produced electrophysiological changes that are reversed by smoking or nicotine.

EEG desynchronization or increased beta power was observed in smokers after smoking a tobacco cigarette (Hauser et al. 1958; Wechsler 1958; Bickford 1960; Ulett and Itil 1969). These findings essentially replicated the animal studies of nicotine. Using power spectral analysis, Ulett and Itil (1969) also observed a decrease in theta power and an increase in alpha frequency. The increase in alpha frequency was previously noted with visual inspection by Lambriase. However, the increase in theta was not. The subjects in the study by Ulett and Itil had smoked one pack or more of cigarettes/day and had been deprived of tobacco cigarettes for 24 hr when the baseline EEG was recorded. Comparisons of the postsmoking EEG were made with this baseline period. Therefore, the decrease in alpha frequency and increase in theta power relative to the data from the postsmoking session may be the result of nicotine deprivation (Chapter IV).

Knott and Venables (1978) compared the alpha frequencies of nonsmokers, 12-hr nicotine-deprived smokers, and nondeprived smokers. They observed a decrease of about 1 Hz in the dominant alpha frequency of the deprived smokers relative to the nonsmokers and nondeprived smokers in a passive eyes-closed situation. An active behavioral task and other frequencies of the EEG were not studied. Knott and Venables hypothesize that smokers were constitutionally different from nonsmokers. The slower alpha frequency was interpreted as an arousal deficit, and smoking as compensation to reduce the arousal deficit. Knott and Venables (1978) and Ulet and Itil (1969) both found an attentional deficit during tobacco deprivation.

Herning and coworkers (1983) investigated the EEG changes related to cigarette smoking in a hospitalized group of healthy smokers who smoked at least a pack and a half of tobacco cigarettes with a machine nicotine delivery of 0.8 mg or more. A serial subtraction task was administered and EEGs were recorded from subjects in an eyes-open state. Alpha frequency was not affected by periods of smoking and deprivation. However, theta and alpha power increased during periods of deprivation and decreased after smoking tobacco but not placebo cigarettes. The effects were most pronounced on theta power. Increases in theta power occurred as early as 30 min after the last cigarette, and were of the same magnitude as those after 10 to 19 hr of nicotine deprivation. The increase in EEG theta was interpreted to be a sign of tobacco deprivation (Chapter IV).

An indirect method of observing an increase in cortical activation was the measurement of alpha power changes after tobacco smoking. A number of investigators reported a decrease in alpha power or abundance with cigarette smoking (Murphree, Pfeiffer, Price 1967; Philips 1971; Caille and Bassano 1974, 1976; Murphree 1979; Herning, Jones, Bachman 1983; Cinciripini 1986), with nicotine

polacrilex gum (Pickworth, Herning, Henningfield 1986, in press), and with i.v. doses of nicotine (Lukas and Jasinski 1983). In spite of differences in the number of cigarettes regularly smoked by the subjects, the length of tobacco deprivation, the type of tobacco cigarette smoked during the experiment, and the route of administration, nicotine reduced alpha power.

Brown (1968) measured the resting EEG for heavy smokers and nonsmokers. No cigarettes were smoked. The EEG of the heavy smokers had less alpha and more beta activity. Twelve hours of nonconfirmed deprivation in the heavy smokers did not change the EEG patterns.

The EEG of neonates of mothers who smoke is not different from that of neonates of control mothers (Chernick, Childiaeva, Ioffe 1983). Whether acute periods of smoking may affect the EEG of the child before birth is not known.

In limited animal and human work, individual or species differences in the effects of nicotine on the EEG have been observed. Nicotine produced a dose-dependent cortical EEG desynchronization in C3H mice and an increase in synchronized EEG similar to hippocampal theta activity in C57BL mice (Erwin, Cornell, Towell 1986). Both effects have been observed at different doses in the same preparation (Kawamura and Domino 1969). Lower doses produce EEG desynchronization, and higher doses produce hippocampal theta. Tobacco cigarette smoking decreased EEG alpha power in Type A subjects and increased theta power in Type B subjects deprived of nicotine for about 4 hr (Cinciripini 1986). The relationship between hippocampal theta in animals and cortical theta in humans is not yet understood. In nondrugged animals cortical desynchronization and hippocampal theta activity often occur simultaneously. Nicotine at low doses produces cortical desynchronization and at high doses produces both types of EEG activity. Animal data indicate that nicotine has effects on at least two systems in the brain: a midbrain area responsible for EEG desynchronization and a limbic system generating hippocampal theta activity. These findings are consistent with the observation that some smokers indicate that they smoke for nicotine's stimulating effects and others smoke for its sedating effects.

Sensory Event-Related Potentials

In animals and humans, the brainstem auditory-evoked potential technique provides a noninvasive method for studying the effects of nicotine on primary auditory sensory function. In the rat, nicotine reduced the amplitudes of Waves III and IV of the brainstem auditory-evoked response (BAER) (Bhargava and McKean 1977; Bhargava, Salamy, McKean 1978; Bhargava, Salamy, Shah 1981). Serotonergic mechanisms may mediate the nicotine-induced reduc-

tion in latency. Lavernhe-Lemaire and Garand (1985) found essentially the opposite. Nicotine increased Waves I-III and did not decrease Waves IV and V of BAER.

Auditory event-related potentials (AERPs) recorded directly from the cortex of rat have provided conflicting information about nicotine's effects on auditory transmission from the inferior colliculus to the cortical areas. Guha and Pradhan (1976), using pentobarbital anesthesia, found a dose-dependent increase in P1 (40 ms) and N1 (110 ms) of the AERP. Bhargava, Salamy, and McKean (1978), using chloralose anesthesia with atropine pretreatment, reported no nicotine-related change in P1 (11 ms), N1 (28 ms), P2 (75 ms), and N2 (121 ms) of the AERP.

After smoking, the P1 (50 ms) of the human AERP is increased during passive tasks at all intensity levels and the N1 (110 ms) is increased in both passive and active tasks (Knott 1985). The N2 (about 215 ms) to P2 (about 260 ms) component of the AERP recorded during a passive task was reduced after cigarette smoking when compared with data from the baseline deprivation test (Friedman and Meares 1980). P2 was also reduced by nicotine in the study by Knott (1985). These components also increased in amplitude as the tobacco deprivation period was lengthened. Any attempt to relate this finding to results in the anesthetized rat would be speculative because AERPs recorded from the cortex of unanesthetized animals and humans are difficult to compare (Wood et al. 1984). Alterations in AERP components in the 75- to 150-ms latency range have been attributed to change in attention. The decrease in the later N2-P2 component is more likely to reflect reduced habituation to auditory stimuli.

The effects of nicotine on visual event-related potentials (VERPs) are more complicated than those on the AERPs. In unaesthetized rabbits, i.v. nicotine (0.025 to 0.500 mg/kg) produced a complex VERP change (Sabelli and Giardini 1972). At 2 min, nicotine depressed the P1 (100 ms) and the N1 (250 ms). At 5 min, these components were enhanced. At doses below 0.050 mg/kg, the N1 was again depressed from 10 to 20 min after the injection. Pretreatment with catecholamine inhibitors diminished the nicotine-induced VERP changes. The authors suggested that the effect of nicotine on VERPs was mediated in part by catecholaminergic mechanisms.

The effects of nicotine on the human VERP using multiple flash intensities were the focus of four studies. The studies were designed to test Buchsbaum and Silverman's (1968) concept of stimulus intensity control and its modulation by nicotine. According to their theory, sensory processing in different individuals varies in at least two ways. Some persons, "augmenters," are more sensitive to higher intensities than to lower intensities, and others, "reducers," are more sensitive to lower than to higher intensities. Smokers might be

one particular type of stimulus processer and may smoke to alter or normalize stimulus intensity. In all studies the comparison was between results after 12 hr or more of unconfirmed tobacco deprivation and those after recent smoking. Components of the VERP increased after smoking in three studies (Hall et al. 1973; Friedman and Meares 1980; Woodson et al. 1982) but decreased in another study (Knott and Venables 1978). The increases and decreases occurred in components of the same latency range (75 to 250 ms) after flash onset. The fourth study differed only slightly from the others in that it used a between-subjects and not within-subject experimental design. Using a single flash intensity, Vasquez and Toman (1967) also observed a decrease in components IV (^{14}0 ms) and V (170 ms) of the VERP when compared with results after 36 hr of tobacco deprivation. Two studies found a nicotine-induced increase at earlier components (III-IV and IV-V) for the lower intensities only. The other study reported an increase in later components (V-VI and VI-VII) at the higher flash intensities. Knott and Venables (1978) observed the decrease after smoking in the middle components (IV-V and V-VI) for the lower intensities. Because of these divergent results, it is premature to conclude that smokers are exclusively augmenters or reducers who are attempting to optimally adjust stimulus intensity by smoking.

Cognitive Event-Related Potentials

Cognitive event-related potentials reflect neural events which appear to be related to different aspects of cognition, such as attention and stimulus evaluation. They usually follow the sensory components of event-related potentials when human subjects are performing active behavioral tasks. They provide information not normally available from performance measures such as reaction time. Increases or decreases in these potentials after smoking can aid in our understanding the effects of nicotine on performance.

When two task-relevant stimuli are separated by a short interval (1 to 3 sec), a negative slow wave develops between them. In particular, this contingent negative variation (CNV) develops in warned or cued reaction times, successive discrimination, and some language processing tasks. The CNV appears to reflect brain preparation to process and respond to the second stimulus. Smoked tobacco and i.v. nicotine either increase or decrease the CNV (Ashton et al. 1973, 1974, 1980; Minnie and Comer 1978). Extraverted smokers took longer to smoke and nicotine increased the CNV. Introverted subjects smoked faster and nicotine decreased the CNV. Reaction time was inversely correlated with CNV amplitude; that is, shorter reaction time was associated with larger CNV. With i.v. doses of nicotine (12.5 to 800.0 μg), larger doses produced a decrease and small doses produced an increase in the CNV in the same

subject. O'Connor (1982) studied the effects of smoking on the orienting (O wave) and expectancy (E wave) components of the CNV in introverted and extraverted subjects. The O wave was not affected by smoking. The E wave, recorded in frontal areas, was increased in extraverted subjects after smoking. The E wave has been interpreted by some investigators as cortical preparation for a response. Smoking decreased a positive parietal E wave in introverts. Nicotine's effect on the E wave suggests the possible enhancement of motor preparation in the extraverted subjects. The decrease of parietal positivity indicates a possible enhancement of stimulus-processing capacities in the introverts.

Poststimulus components P2(00) and P3(00) were affected by cigarette smoking and nicotine polacrilex gum. P2 is thought to be an index of habituation (Hillyard and Picton 1979), and P3 an index of stimulus evaluation (Johnson 1986). Both components were reduced in deprived smokers after smoking (Knott 1985; Herning and Jones 1979). Knott (1985) interprets the reduction in P2 as a more efficient habituation of sensory screening of relevant stimuli. The reduction in P3 amplitude after smoking indicates a poorer evaluation of task-relevant stimuli. The P3 latency and reaction time were reduced only by cigarettes with higher machine-tested nicotine yields (Edward et al. 1985). Such data indicate faster stimulus and response processing. These authors did not report any P3 amplitude changes. If none were present or P3 was reduced, the argument for enhanced stimulus processing would be weak. Herning and Pickworth (1985) reported both dose-dependent increases and decreases in P3 amplitude as a function of background noise levels when deprived smokers chewed nicotine polacrilex gum (4 mg and 2 mg doses). The respective increase or decrease was blocked by mecamylamine pretreatment. Thus, the effect of nicotine on stimulus evaluation remains unclear and is perhaps confounded by cognitive deficits after periods of nicotine deprivation.

Motor Potentials

O'Connor (1986) investigated the effect of tobacco smoking on motor potential and motor performance. Smoking increased the motor readiness potential in extraverts, but not in introverts. These results are consistent with his earlier finding of an increased E wave in extraverts after smoking. For introverts, smoking improved task performance, but did not increase the motor readiness potential.

Other Peripheral Effects Relevant to Tobacco Use

In addition to vast central and peripheral effects, cigarette smoking and nicotine have other peripheral effects that may contribute to tobacco use. These additional factors have received less

research attention, mainly because they involve relatively new theory or methodological approaches. For example, there is evidence that direct stimulation of the trachea is important for cigarettes to satisfy smokers (Rose et al. 1984) (Chapter IV). There is also evidence that nicotine acts directly on the lung to stimulate afferent neurons that, in turn, result in skeletal muscle relaxation and electrocortical arousal (Ginzel 1987). These effects may contribute to the relationship between smoking and stress (Chapter VI). Other research indicates that smoking affects psychophysiological reactivity, an integrative mechanism that is different from the classic, physiological approach of examining individual systems or pathways. Therefore, psychophysiological reactivity and its relevance to smoking are discussed.

Psychophysiological Reactivity and Smoking

Psychophysiological reactivity is emerging as a useful construct in smoking research, linking basic biological processes (genetic vulnerability, central neurochemical factors) to behavioral coping and other psychosocial factors. Psychophysiological reactivity refers to a physiological response to a specific stimulus or as a result of the absence of stimulation. This response can, in some cases, act as a stressor. Within the broader conceptual framework of a stress-coping model of smoking addiction (Shiffman and Wills 1985), smoking behavior can be viewed both as a potential stimulus and as a coping response that modulates psychophysiological reactivity.

Studies of psychophysiological reactivity illustrate the value of controlled laboratory procedures to study person-environment interactions. Psychophysiological reactivity reflects an interaction of the organism and the environment. It is affected by individual differences in multiple response modes (physiological, cognitive, behavioral) and takes into account the genetic and learning history and current state of the organism.

This Section reviews two separate but interrelated lines of psychophysiological reactivity research with humans. The first is the effect of smoking on psychophysiological reactivity. Related issues include identification of mechanisms that may help to reveal why some individuals smoke and the relationship between smoking and coronary heart disease (CHD). The second research line addresses the relationship among situational events (general and drug-specific), psychophysiological reactivity, and relapse.

The effects of smoking on the cardiovascular aspects of physiological reactivity have been well documented and appear to be primarily due to effects of nicotine and carbon monoxide (Suter, Buzzi, Bättig 1983; Koch et al. 1980; Rosenberg et al. 1980). In individuals with no cardiovascular disease, some of the typical effects of smoking and nicotine are elevated heart rate and blood pressure and a fall in

fingertip temperature and capillary blood flow (Richardson 1987; Ashton et al. 1982; Epstein and Jennings 1986; Henningfield et al. 1983).

Accompanying cardiovascular reactions to smoking are cognitive reactions, including perceptions of relaxation, and anxiolytic, antinociceptive, euphoric, stimulative, and dysphoric effects (Kozlowski, Director, Harford 1981). Although there is consistency in the literature with regard to the self-reported emotional changes experienced as a result of smoking, there are clear differences in response and direction of effects between individuals and within individuals over time (Best and Hackstian 1978; Gilbert 1979; Gilbert and Welser, in press). Smoking can produce physiological changes that are concurrent with subjective tranquilizing effects (Nesbitt 1973; Shiffman and Jarvik 1984; Gilbert 1979). This phenomenon has led investigators to emphasize the importance of incorporating physiological, psychological, and environmental factors into more biobehavioral models to better understand the cognitive and physiological components of reactivity to smoking (Pomerleau and Pomerleau 1984; Baum, Grunberg, Singer 1982; Abrams et al. 1987; Grunberg and Baum 1985). For example, nicotine has direct and indirect actions on central neuroregulatory systems and has biphasic effects of both stimulation and blockade. These factors can help explain effects such as the anxiolytic and antinociceptive phenomena (Pomerleau 1986) at a cognitive and neurochemical level, while at the same time resulting in increased heart rate and blood pressure and decreased perception of muscle tension (Epstein et al. 1984).

In addition to dosage, biphasic, and physiological factors, the influence of setting and expectancy set, the current state of the individual (smoking, deprived, stressed, not stressed), and individual differences in dependence, genetic, demographic, and learning history can all influence psychophysiological reactivity. For example, smoking a 1.3-mg-nicotine cigarette under conditions of mild sensory isolation produced consistent arousal effects (i.e., elevations in heart rate and skin conductance level with decreases in EEG alpha waves) in smokers compared with sham smoking or a situational control group. However, under conditions of stress, as induced by intermittent noise bursts, a mixed stimulant (heart rate) and depressant (EEG, skin conductance) response was observed (Golding and Mangan 1982). Woodson and coworkers (1986) also reported that during noise, smoking induced cardiovascular stimulation (i.e., heart rate acceleration, peripheral vasoconstriction) but electrodermal depression (i.e., lowered skin conductance response amplitude). These findings are consistent with the conclusions of Gilbert and Welser (in press) that unidimensional models are inadequate to explain the effects of smoking.

In addition to research on the impact of smoking on psychological and physiological processes, studies have also examined the combined cardiovascular effects of smoking and stress. In this context the concept of cardiovascular psychophysiological reactivity is used to help clarify the relationship among stress, smoking, and CHD (Epstein and Jennings 1986). MacDougall and colleagues (1983) randomly assigned 51 male smokers to smoking versus sham smoking and stress versus no stress conditions in a 2 x 2 factorial design. The stressor was a difficult video game performed under challenging conditions. Subjects who sham smoked under no stress showed minimal cardiovascular response. Subjects who smoked under no stress or who sham smoked under stress evidenced similar degrees of response of about a 15-bpm increase in heart rate, a 12-mmHg increase in systolic blood pressure, and a 9-mmHg increase in diastolic blood pressure. Subjects in the combined smoking and stress condition had larger increases in all cardiovascular measures. The combination of mild stress and smoking produced effects that were twice those of either condition alone. Smoking and stress combined to increase cardiovascular response in men.

In a followup study of women, using the same 2 x 2 factorial design, Dembroski and colleagues (1985) found that the combined effect of stress and smoking produced blood pressure and heart rate increases that exceeded the sum of the individual effects. However, because modifications were made in dosage and psychological challenge, the two studies were not identical. The gender differences noted could therefore reflect methodological differences, uncontrolled factors, or possibly differences between the sexes in response to the stress and smoking stimuli. Indeed, it has been noted that females may be more likely than males to smoke to regulate affect (Ikard and Tomkins 1973), are more likely to relapse after quitting (Gritz 1986), may differ in biological factors relating to stress reactivity/sensitivity (Abrams et al. 1987), and show greater changes in body weight and eating behavior in response to nicotine (Grunberg, Bowen, Winders 1986; Grunberg, Winders, Popp 1987). (See Chapter VII for a discussion of treatment implications of these possible sex differences.)

In a conceptually related study, the relationship between physiological responses to cognitive (mental arithmetic) and physical (cold pressor) stressors was examined in female smokers and nonsmokers who either used or did not use oral contraceptives (Emmons and Weidner, in press). All subjects showed some physiological response (heart rate and blood pressure responses) to the stressors, but in smokers oral contraceptive use significantly enhanced the systolic blood pressure response to cognitive stress. This finding may be related to the fact that smokers who use oral contraceptives are 5.6-times more likely to have a myocardial infarction than are smokers

who do not use oral contraceptives, 9.7-times more likely than nonsmoking users, and 39-times more likely than nonsmokers who do not use oral contraceptives (Shapiro et al. 1979; Jain 1976; Ory 1977).

In studies of psychophysiological reactivity, it is critical to identify, measure, and control for factors that might confound or alter the intended impact of the independent variables. For instance, time since last drink and beliefs, expectations, and setting are important variables to consider in the study of alcohol addiction (Abrams and Wilson 1979; Abrams 1983; Marlatt and Rohsenow 1980). The 2 x 2 balanced placebo design (Marlatt, Demming, Reid 1973), where expectancy set (told to expect the drug or told to expect no drug) and actual content (drug versus placebo) are fully controlled, has been used extensively in the alcohol addiction field to isolate the separate and interactive elements of cognitive and pharmacologic effects. With smoking, little is known about the separate and interactive impacts of expectations of cigarettes' effects versus their actual pharmacologic effects. This is partially because it is difficult to find a method of administration that closely resembles smoking but where the required manipulations to achieve a credible balanced placebo design can be accomplished.

Another methodological concern is control over the dosage of nicotine absorbed by the smoker. Nicotine is thought to be the most important tobacco constituent responsible for the acute effects of smoking on reactivity, attention and task performance, mood, and withdrawal following cessation (Perkins et al., in press; Pomerleau, Turk, Fertig 1984; Hughes et al. 1984). However, in tobacco smoking, nicotine is accompanied by more than 4,000 other compounds (Dube and Green 1982) and smokers are known to smoke in individualized ways (Epstein et al. 1981) (Chapter IV). The coaching of puff frequency and other attempts to standardize intake of smoke are imperfect (Perkins et al., in press). An aerosol nasal spray appears to be a promising alternative to smoking in studies of behavioral and physiological effects. It allows for rapid uptake through inhalation, and a dose-response study indicates patterns of heart rate, blood pressure, and serum nicotine levels that are very similar to those obtained by smoking cigarettes of equivalent nicotine content (Perkins et al., in press).

Perkins and coworkers (in press) studied the separate and interactive effects of nicotine administered by nasal aerosols and stress on psychophysiological reactivity. The authors note that the previous studies (MacDougall et al. 1983; Dembroski et al. 1985) could be confounded because smokers usually smoke more under stress and therefore they may inhale more nicotine or alter their smoking in other ways when stressed (Mangan and Golding 1978; Rose, Ananda, Jarvik 1983) (Chapter VI). In other words, the additive effects of

stress and smoking on physiological responses could have resulted from uncontrolled changes in smoking pattern between the smokers in the no-stress and stress conditions. Perkins and colleagues (in press) studied 12 male smokers in a repeated-measures design, where subjects received all 4 conditions (stress plus nicotine, stress plus placebo, rest and nicotine, and rest and placebo) on separate days with the order of condition counterbalanced within subjects. Following the methodology of previous studies of psychophysiological reactivity, the researchers used an active stressor consisting of a video game under conditions of competitive challenge. Nicotine was administered in measured 1.0-mg doses by the aerosol nasal method (Perkins et al., in press). Consistent with observations of MacDougall and coworkers (1983), results were additive for heart rate reactivity. However, effects were less than additive for systolic and diastolic blood pressure.

Taken together, the studies of the effects of smoking cigarettes and of nicotine aerosol stimuli on the physiological responses of adult males demonstrate a consistent effect for the stimuli alone, additive in combination with stress on heart rate, and additive or less than additive with stress on blood pressure. There is some suggestion that effects may be more than additive for women, but this finding requires replication.

Psychophysiological Reactivity, Smoking Cessation, and Relapse

Psychophysiological reactivity also serves as a conceptual framework to study relapse after cessation from smoking (Shiffman 1986b; Abrams 1986). Individual differences in psychophysiological reactivity and associated coping responses, as a function of general and smoking-specific stressful stimuli, have been hypothesized to mediate relapse. For example, smokers who smoke more when stressed might be particularly vulnerable to relapse (Pomerleau, Adkins, Pertschuck 1978). This idea is consistent with the observation that relapse may be triggered by life stress events and other psychosocial demands (Ockene et al. 1982) and by high-risk situations including negative emotions, social conflicts and pressures, and the presence of alcohol or smoking cues (Marlatt and Gordon 1985; Shiffman 1979, 1982, 1984, 1986a; Abrams et al. 1986). If certain psychophysiological reactivity responses distinguish potential abstainers from relapsers, cessation may be better maintained by identifying "relapse-prone" individuals (Chapter VII).

Stressful environmental demands, sensitivity of the individual to these demands, and the repertoire of coping responses are important factors in relapse (Shiffman and Wills 1985; Abrams et al. 1987). These same factors also may contribute to initiation of smoking among adolescents. Wills (1985) provides evidence for the stress-

coping model of smoking in adolescence, relating both stress and coping patterns to substance use. Results are consistent with other findings that, in addition to peer pressure to smoke, adolescents actively seek methods of coping with their perceptions of stress (Wills 1985; Friedman, Lichtenstein, Biglan 1985; Botvin and McAlister 1981). Although these survey studies are consistent with the notion of smoking as a means of coping with psychophysiological reactivity to environmental demands, research has not yet measured reactivity in adolescents prior to smoking onset.

Observational and retrospective studies of relapse have identified other smoking-specific stressful stimuli and cognitive/psychophysiological measures of reactivity that are relevant to relapse. Situations or stimuli that cue smoking and are associated with relapse include pharmacologic dependence and withdrawal symptoms (Jarvik 1977; Pomerleau and Pomerleau, in press; Hughes et al. 1984), stimuli previously associated with smoking (e.g., coffee drinking, alcohol) (Shiffman 1984, 1986a; Best and Hakstian 1978), and urges to smoke (Myrsten, Elgerot, Edgren 1977). Situational stimuli may or may not have previously been paired with smoking and may or may not include smoking cues as a trigger for relapse.

Substance use cues themselves (e.g., the sight and smell of cigarettes) also may precipitate relapse, perhaps in combination with other stressful stimuli or in a vulnerable individual (Shiffman 1986b; Abrams et al. 1987). Models of how substance use cues are related to relapse have been proposed on the basis of classical, operant, and social learning principles. Reactions may be conditioned to stimuli repeatedly paired with smoking, resulting in craving and physiological reactivity in their presence and moderated by dependence, tolerance, and nonpharmacologic withdrawal (Siegel 1983; Cooney, Baker, Pomerleau 1983; Gritz 1980). Psychophysiological reactivity to smoking cues could mimic the prior drug response (Wikler 1965), result in a drug-opposite (compensatory) response (Siegel 1983), or have other effects on psychological processes such as perceived anxiety, urges to smoke, and self-efficacy in resisting relapse according to a social learning model of relapse (Marlatt and Gordon 1985).

Abrams and colleagues (1987) studied the psychophysiological reactivity and behavioral coping responses of male and female relapsers and quitters in four simulated situational contexts: general social situations, smoking-specific negative emotional and interpersonal role-plays, high-demand social stress, and relaxation. Compared to abstainers, relapsers had higher heart rates and higher perceived anxiety and were rated as less skillful at coping in the smoking-specific intrapersonal (negative affect) situations. There were no differences on any measures in the high-performance-demand general-social-stress procedure. There were some differences

in heart rate and self-reported anxiety in the general social situations and in heart rate in the relaxation interval, with relapsers having higher levels than abstainers. Abstainers and relapsers did not differ in heart rate, perceived anxiety, or coping skills in the high-demand social anxiety procedure, but they did differ in the other situations. The results suggest that selected situational demands prompt situation-specific psychophysiological changes.

Rickard-Figueroa and Zeichner (1985) used a within-subjects design to examine the responses of smokers to a confederate of the experimenter lighting and smoking the subject's preferred brand of cigarette behind a glass window. Cigarette paraphernalia were placed adjacent to the subject but smoking was not permitted until after the session. The cue exposure manipulation resulted in higher urges to smoke, increased systolic and diastolic blood pressure, and increased heart rate variability compared with a no-cue condition. Urges were significantly positively correlated with diastolic blood pressure, the use of active mastery to cope with urges, and the more rapid smoking of a standard cigarette after the trial.

In a study that shows some evidence for a conditioned response, Saumet and Dittmar (1985) measured finger-pulse amplitude, a measure of peripheral vasoconstrictive activity, while subjects placed an unlit cigarette into their mouths and waited for it to be lit. Heavy smokers showed an anticipatory vasoconstrictive response to the cigarette compared with light smokers and nonsmokers.

Abrams and colleagues (in press) used smoking cues and a social stressor to simulate an interpersonal situation with high risk for relapse. Relapsers, abstainers, and never smokers were examined for psychophysiological reactivity. Compared with controls (never smokers), relapsers had significant heart rate reactivity, stronger urges to smoke, and subjective anxiety. Trained raters, unaware of subject smoking status, judged relapsers as having significantly less effective coping skills to resist smoking. In a second study, the same assessment was used prospectively in a treatment outcome context to determine whether patterns of psychophysiological reactivity could discriminate between quitters who maintain abstinence from those who do not. Both heart rate reactivity and subjective anxiety were greater in quitters who relapsed at 6-month followup compared with those who continued to abstain. The groups did not differ with regard to urges to smoke or behavioral judgments of coping skill. Thus, the two studies were consistent for heart rate and perceived anxiety but not for urges or objective ratings of coping effectiveness.

In a reanalysis of the heart rate data from Abrams and coworkers (in press), Niaura and colleagues (in press) examined beat by beat event-related heart rate during the period immediately before and for the 10 sec following the lighting of a cigarette by a confederate (subjects did not smoke throughout). Prospective relapsers showed a

strong decelerative trend at the point of lighting, whereas prospective abstainers did not. The results may reflect a conditioned compensatory response (Siegel 1983) or some other information processing/attentional phenomenon (Sokolov 1963; Knott 1984). In another treatment study, Emmons (1987) examined smokers' cardiovascular reactivity to mental arithmetic or deep knee bends before and 6 months after smoking cessation. There was no change in reactivity (heart rate, systolic and diastolic blood pressure) to either stressor before and after quitting. Heightened pretreatment heart rate reactivity significantly discriminated relapse at 6-month follow-up.

Individual differences in psychophysiological reactivity may influence the likelihood of relapse. This possibility is discussed in Chapter VII.

Summary and Conclusions

1. Nicotine is a powerful pharmacologic agent that acts in the brain and throughout the body. Actions include electrocortical activation, skeletal muscle relaxation, and cardiovascular and endocrine effects. The many biochemical and electrocortical effects of nicotine may act in concert to reinforce tobacco use.
2. Nicotine acts on specific binding sites or receptors throughout the nervous system. Nicotine readily crosses the blood-brain barrier and accumulates in the brain shortly after it enters the body. Once in the brain, it interacts with specific receptors and alters brain energy metabolism in a pattern consistent with the distribution of specific binding sites for the drug.
3. Nicotine and smoking exert effects on nearly all components of the endocrine and neuroendocrine systems (including catecholamines, serotonin, corticosteroids, pituitary hormones). Some of these endocrine effects are mediated by actions of nicotine on brain neurotransmitter systems (e.g., hypothalamic-pituitary axis). In addition, nicotine has direct peripherally mediated effects (e.g., on the adrenal medulla and the adrenal cortex).

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